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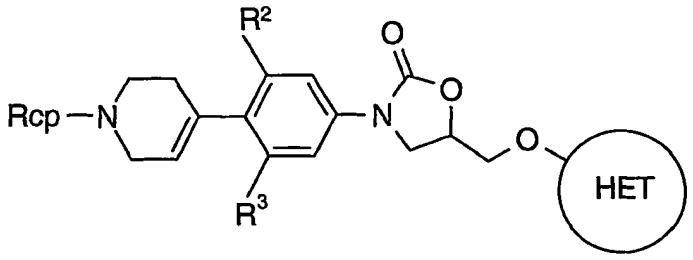
(54) Title: PROCESS FOR PHOSPHORYLATION

(57) Abstract: A method for preparing a compound having a terminal group of formula $(HO)_2OPO\text{-}CH_2CH(OH)\text{-}CO\text{-}$, which method comprises treating a species of formula $(R^6O\text{-}CH_2CH(OP(O)(OR^7)_2CO\text{-})$ where R^6 is a protecting group, and each group R^7 is hydrogen or a protecting group with acid in the presence of water to remove any protecting groups R^6 and R^7 and rearrange the secondary phosphoryl group to a primary phosphoryl group. The process is particularly useful in the preparation of certain antibacterial oxazolidinone compounds.

PROCESS FOR PHOSPHORYLATION

The invention relates to chemical processes for the preparation of certain oxazolidinone anti-Gram positive bacterial agents.

In our International Patent Application No. WO 99/64417 we describe a new class of antibacterial oxazolidinone compounds which are effective as anti-Gram positive bacterial agents, and certain processes for their preparation. These include compounds of formula (I):



(I)

wherein

HET is a C-linked 5-membered heteroaryl ring containing 2 to 4 heteroatoms independently selected from N, O and S, which ring is optionally substituted on an available carbon atom by 1 or 2 substituents independently selected from (1-4C)alkyl, amino, (1-4C)alkylamino, (1-4C)alkoxy and halogen, and/or on an available nitrogen atom (provided that the ring is not thereby quaternised) by (1-4C)alkyl;

R^2 and R^3 are independently hydrogen or fluoro;

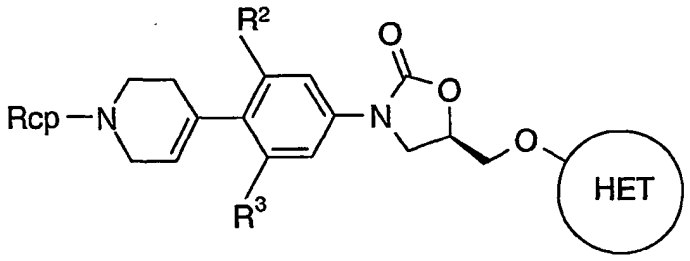
Rcp is of the formula $R^{13}CO$- (wherein R^{13} is (1-10C)alkyl substituted by two or more hydroxy groups; 2 of which are in a 1,2-diol orientation, ie. there is a terminal primary alcohol with an adjacent secondary alcohol), or pharmaceutically-acceptable salts, or in-vivo-hydrolysable esters thereof.

It is to be understood that all terms used in the definition of formula (I) above are as defined in WO 99/64417.

Of the above compounds, those in which HET is (unsubstituted) isoxazol-3-yl, 1,2,4-oxadiazol-3-yl, isothiazol-3-yl or 1,2,5-thiadiazol-3-yl are preferred.

Of the compounds of formula (I), those of formula (I-1) are the pharmaceutically active anti-bacterial enantiomer. The pure enantiomer depicted in (I-1), or mixtures of the 5R and 5S enantiomers, for example a racemic mixture are included in WO 99/64417. If a mixture of enantiomers is used, a larger amount (depending upon the ratio of the

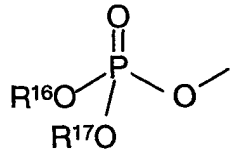
enantiomers) will be required to achieve the same effect as the same weight of the pharmaceutically active enantiomer. For the avoidance of doubt the enantiomer depicted below is the 5R enantiomer.



(I-1)

Furthermore, some compounds of the formula (I) and (I-1) may have other chiral centres, and such optical and diastereo-isomers, and racemic mixtures may possess antibacterial activity. It is well known in the art how to prepare optically-active forms (for example by resolution of the racemic form by recrystallisation techniques, by chiral synthesis, by enzymatic resolution, by biotransformation or by chromatographic separation) and how to determine antibacterial activity.

In-vivo hydrolysable esters include compounds of formula (I) and (I-1) in which any free hydroxy group independently forms a phosphoryl ester of the formula (PD3) :



(PD3)

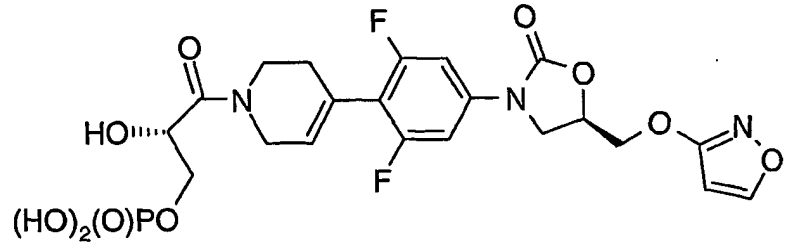
where R^{16} and R^{17} are independently selected from hydrogen or a pharmaceutically acceptable cation as described hereinafter, such as an alkaline metal ion such as sodium or potassium, to give a pharmaceutically acceptable salt.

Suitable pharmaceutically-acceptable salts include base salts such as an alkali metal salt for example sodium or potassium, an alkaline earth metal salt for example calcium or magnesium, an organic amine salt for example triethylamine, morpholine, N-methylpiperidine, N-ethylpiperidine, procaine, dibenzylamine, N,N-dibenzylethylamine, tris-(2-hydroxyethyl)amine, N-methyl deglucamine, piperazine, and amino acids such as lysine and arginine. There may be more than one cation or anion depending on the number of charged functions and the valency of the cations or anions. A preferred pharmaceutically-acceptable salt is the sodium salt. Another preferred pharmaceutically acceptable salt is the

potassium salt.

However, to facilitate isolation of the salt during preparation, salts which are less soluble in the chosen solvent may be preferred whether pharmaceutically-acceptable or not.

Of the above compounds of formula (I) and (I-1), 5(R)-isoxazol-3-yloxymethyl-3-(4-(1-(2(S)-hydroxy-3-phosphoryl-propanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one of formula (A) and salts are especially preferred.



A

Our co-pending International Patent Application No. PCT/GB00/04527 (WO 01/40236) describes and claims a modified route to certain prodrugs of the compounds of formula (I). In particular, that application is concerned with the production of phosphate prodrugs of compounds of formula (I) such as the compound of formula (A) above. The process described there involves a phosphorylation, deprotection and rearrangement. Specifically, a phosphate is produced by the formation of a primary mono-phosphoryl (-$OPO(OH)_2$) group in a terminal 1,2-diol-propanoyl (HO-$CH_2CH(OH)$-CO-) functionality comprising the steps of

(i) formation of a protected primary 1,2-diol species (PgO-$CH_2CH(OH)$-CO-);

(ii) formation of a secondary phosphoryl group (optionally protected) and

(iii) treatment of this secondary phosphoryl group with acid to deprotect the protected primary alcohol function and rearrange the secondary phosphoryl group to a primary phosphoryl group (to give a $(HO)_2OPO$-$CH_2CH(OH)$-CO- functionality); wherein Pg is a protecting group, such as (1-6C)alkyl and in particular butyl.

The reaction is illustrated for the preparation of the preferred compound A as shown in the Reaction Scheme in this application, which is Scheme 2B in copending International Patent Application No. WO 01/40236.

The applicants have found surprisingly that the yield and purity of compounds such as compound A (2F in Reaction Scheme) above, can be increased by adding a small and

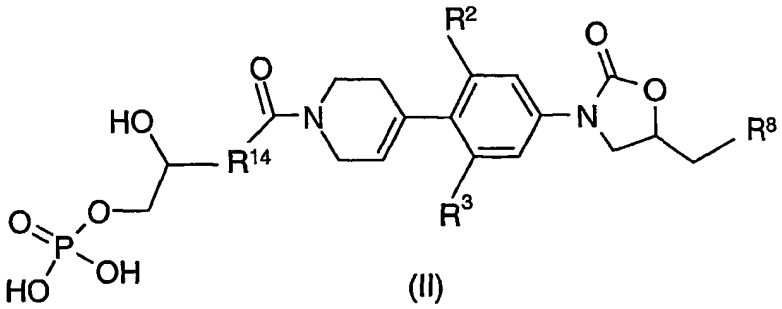
controlled amount of water during the rearrangement stage of the procedure. This finding is quite unexpected in view of the hydrolytic instability of the compounds involved.

According to the present invention there is provided a method for preparing a compound having a terminal group of formula $(HO)_2OPO\text{-}CH_2CH(OH)\text{-}CO\text{-}$, which method comprises treating a species of formula $(R^6O\text{-}CH_2CH(OP(O)(OR^7)_2CO\text{-})$ where R^6 is a protecting group, and each group R^7 is hydrogen or a protecting group with acid in the presence of water to remove any protecting groups R^6 and R^7 and rearrange the secondary phosphoryl group to a primary phosphoryl group.

The applicants have found that by introducing small quantities of water into the reaction mixture, a better yield of the desired product in obtained, with fewer phosphate by-products.

Suitable protecting groups R^6 and R^7 include (1-6C)alkyl and in particular tertiary butyl.

The method of the invention is suitably applied to compounds similar to formula (I) above. Thus in particular, the invention provides a method of producing a compound of formula (II)



(II)

or a salt thereof, wherein

R^8 is $-OR^9$, $-SR^9$, $-NHR^{10}$ or $-NR^{11}R^{12}$, where

R^9 is a C-linked 5-membered heteroaryl ring containing 2 to 4 heteroatoms independently selected from N, O and S, which ring is optionally substituted on an available carbon atom by 1 or 2 substituents independently selected from (1-4C)alkyl, amino, (1-4C)alkylamino, (1-4C)alkoxy and halogen, and/or on an available nitrogen atom (provided that the ring is not thereby quaternised) by (1-4C)alkyl; or

R^9 is a C-linked 6-membered heteroaryl ring containing 1 or 2 nitrogen heteroatoms, which ring is optionally substituted on any available C atom (provided that when the N atom is

adjacent to the link, there is no substitution on any C atom that is adjacent to this N atom) by 1, 2 or 3 substituents independently selected from (1-4C)alkyl, amino, (1-4C)alkylamino, (1-4C)alkoxy, (1-4C)alkoxycarbonyl and halogen;

R^{10} is is a C-linked 5-membered heteroaryl ring containing 2 to 4 heteroatoms independently selected from N, O and S, which ring is optionally substituted on an available carbon atom by 1 or 2 substituents independently selected from (1-4C)alkyl, amino, (1-4C)alkylamino, (1-4C)alkoxy, (1-4C)alkoxycarbonyl and halogen, and/or on an available nitrogen atom (provided that the ring is not thereby quaternised) by (1-4C)alkyl;

or

R^{10} is a C-linked 6-membered heteroaryl ring containing 2 or 3 nitrogen heteroatoms, which ring is optionally substituted on any available C atom by 1, 2 or 3 substituents independently selected from (1-4C)alkyl, amino, (1-4C)alkylamino, (1-4C)alkoxy, (1-4C)alkoxycarbonyl and halogen;

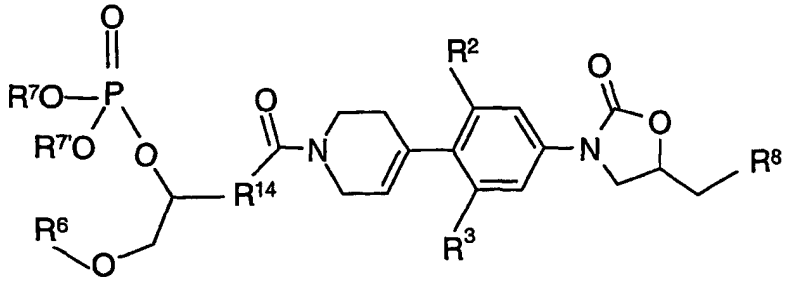
R^{11} and R^{12} together with the nitrogen atom to which they are attached form a 5-membered heteroaryl ring, containing either (i) 1 to 3 further nitrogen heteroatoms or (ii) a further heteroatom selected from O and S together with an optional further nitrogen heteroatom; which ring is optionally substituted on a C atom by an oxo or thioxo group; and/or the ring is optionally substituted on a C atom by 1 or 2 (1-4C)alkyl groups; and/or on an available nitrogen atom (provided that the ring is not thereby quaternised) by (1-4C)alkyl; or

R^{11} and R^{12} together with the nitrogen atom to which they are attached form a 6-membered heteroaryl ring containing up to three nitrogen heteroatoms in total (including the linking heteroatom), which ring is substituted on a suitable C atom by oxo or thioxo and optionally substituted on any available C atom by 1 or 2 (1-4C)alkyl substituents;

R^2 and R^3 are independently hydrogen or fluoro;

R^{14} is a bond or a (1-8C)alkyl group which is optionally substituted by one or more hydroxy groups;

which process comprises reacting a compound of formula (III)



(III)

where R^2, R^3, R^8 and R^{14} are as defined in relation to formula (II), and R^6 is a protecting group and R^7 and $R^{7'}$ are independently selected from hydrogen or a protecting group; with an acid in the presence of water, and thereafter if desired converting the product to a salt.

The acid used in the reaction is suitably a strong mineral acid such as hydrochloric acid, trifluoroacetic acid or sulphonic acid resins (such as Amberlyst resins).

Suitable organic solvents include dioxane and tetrahydrofuran. A preferred solvent is dioxane.

Preferably the reaction is conducted in an organic solvent to which water is added in amounts of from 1 to 10% w/v, preferably from 1-5%w/v, and most preferably at about 3%w/v.

Preferred compounds of formula (II) are as described in WO 99/64417.

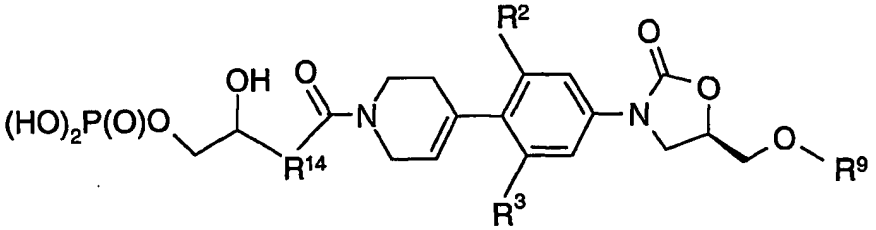
Suitably, in the compound of formula (II), $-R^8$ is $-OR^9$.

Examples of compounds of formula (II) where R^8 is a group $-NR^{11}R^{12}$ are described in copending International Patent Application no. PCT/GB01/01815 (WO 01/81350). Particular examples of group R^8 in this case is N-linked tetrazole or triazole.

Examples of compounds of formula (II) where R^8 is a group $-NHR^{10}$ are shown in WO 00/21960. Particular examples of R^{10} are isoxazol-3-yl, isoxazol-5-yl, 1,2,4-oxadiazol-3-yl, isothiazol-3-yl, 1,2,4-thiadiazol-3-yl or 1,2,5-thiadiazol-3-yl.

In addition, it may be preferred that in the compound of formula (II), R^9 is a C-linked 5-membered heteroaryl ring containing 2 to 4 heteroatoms independently selected from N, O and S, which ring is optionally substituted on an available carbon atom by 1 or 2 substituents independently selected from (1-4C)alkyl, amino, (1-4C)alkylamino, (1-4C)alkoxy and halogen, and/or on an available nitrogen atom (provided that the ring is not thereby quaternised) by (1-4C)alkyl.

Particular examples of compounds of formula (II) are compounds of formula (IV)



(IV)

where

R^2, R^3, R^9 and R^{14} are as defined in relation to formula (II).

Most preferably, in the above compounds R^{14} is a direct bond.

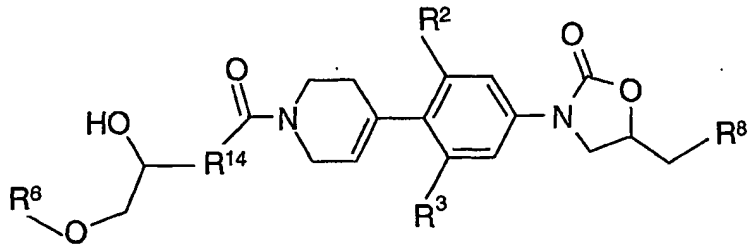
Suitably R^2 and R^3 are fluorine.

A particular example of the R^9 or R^{10} where these are present are isoxazolyl, and particularly isoxazol-3-yl.

Thus a particularly preferred compound of formula (II) is 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2(S)-hydroxy-3-phosphoryl-propanoyl)-1,2,5,6-tetrahydropyridy-4-yl)-3,5-difluorophenyl)oxazolidin-2-one.

Compounds of formula (II) are suitably converted subsequently to salts, preferably pharmaceutically acceptable salts as hereinbefore described, such as sodium salts, using conventional methods. If a salt is not pharmaceutically acceptable, it may be converted to a pharmaceutically-acceptable salt by conventional techniques.

Compounds of formula (III) are suitably prepared by phosphorylation of a compound of formula (V)

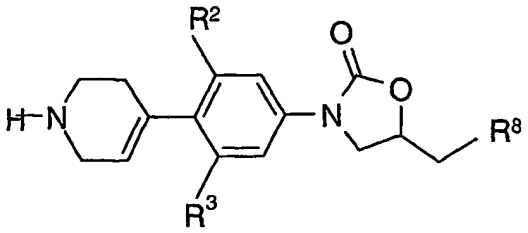


(V)

where R^2, R^3, R^6, R^8 and R^{14} are as defined above.

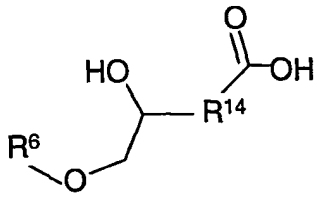
Phosphorylation may be effected using conventional methods, for example by reacting the compound of formula (V) with a protected phosphoramidate such as di-t-butyl-N,N-diethylphosphoramidite in the presence of an activator (such as a triazole, a tetrazole, or a pyridine salt, for example pyridine HCl salt), the product of which is then oxidised for example using hydrogen peroxide, cumene hydroperoxide or MCPBA).

Compounds of formula (V) are suitably prepared by reacting a compound of formula (VI)



(VI)

where R^8, R^2 and R^3 are as defined in relation to formula (II) above, with a compound of formula (VII)



(VII)

where R^{14} is as defined in relation to formula (II) and R^6 is as defined in relation to formula (III). The reaction is suitably effected in an organic solvent such as DMF in the presence of a coupling reagent such as dimethylaminopropyl-ethylcarbodiimide.

Compounds of formula (VI) and (VII) are either known compounds (see for example our WO Patent 92/00276 and WO 99/64417) or they can be prepared from known compounds by conventional methods.

The process of the invention provides good yields of compounds of formula (II) at high purity levels.

The invention will now be illustrated but not limited by reference to the following Preparation, Example and Reaction Scheme.

Preparation

Preparation of 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(3-t-butoxy-2(S)-hydroxypropanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one

Step 1: Preparation of 3,5-Difluoro-4-(1-benzyl-4-hydroxyhexahydropyrid-4-yl)aniline

nBuLi (1.32M in hexanes, 350ml, 0.462 mol) was added dropwise over 20 minutes to a solution of N,N-(1,2-bis(dimethylsilyl)ethane)-3,5-difluoroaniline (108.4g, 0.40mol, J. Org. Chem., 60, 5255-5261 (1995)) in 800ml dry THF at -70°C under argon. After stirring for a further 4 hours at -70°C, N-benzyl-4-piperidone (87.8g, 0.46mol) in 270ml dry THF was

added dropwise over 40 minutes at the same temperature and the reaction allowed to stir to ambient temperature overnight. Solvent was removed in vacuo and the resultant product treated with ice and conc.HCl and extracted with ether. The aqueous acidic phase was then treated with 40% NaOH with cooling, extracted with ether (and worked up by washing with water, with brine and drying with an anhydrous drying agent such as magnesium sulfate or sodium sulfate before evaporation - this work up procedure is referred to as work up in the usual manner hereinafter) to give 144.7g of a sludge. Analysis by TLC using 10% MeOH/dichloromethane on silica indicated that the desired alcohol was present as approximately 90% of the product, and the crude product was used without further purification. MS: ESP+ (M+H) = 319.

Step 2: 3,5-Difluoro-4-(1-benzyl-1,2,5,6-tetrahydropyrid-4-yl)aniline

The crude product from step 1 (144.7g) was suspended in 400ml conc.HCl and heated at reflux with stirring for 18 hours. TLC showed all starting material had reacted, and after cooling in ice the reaction mixture was taken to pH 11 with conc. NH_3 (aq) and extracted three times with dichloromethane. Usual work-up gave 119.5g of a viscous oil. TLC indicated a purity of ca. 80% and the crude product was used without further purification. MS: ESP+ (M+H) = 301.

Step 3: N-Benzyloxycarbonyl-3,5-difluoro-4-(1-benzyl-1,2,5,6-tetrahydropyrid-4-yl)aniline

The crude aniline from step 2 (3.2g, 10.7mmol) in 10ml of acetone was added in one portion to a stirred solution of sodium dihydrogen phosphate (3.0g) in 30ml water. The resulting mixture was cooled to 5-10^{0}C and a solution of benzylchloroformate (2.18g, 1.8ml, 12.8mmol) in 10ml of acetone was added dropwise. The mixture was stirred for a further hour at ice-bath temperature and then at ambient temperature for 2 hours. The mixture was diluted with 80ml water, basified with conc.NH_3(aq) and extracted with EtOAc. Usual work-up gave a viscous oil which was purified by flash chromatography (Merck 9385 silica, EtOAc/isohexane (3:7 eluant) and triturated with isohexane to give a solid (1.53g 33%). MS: ESP+ (M+H) = 434.

Step 4: 5(R)-Hydroxymethyl-3-(4-(1-benzyl-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one

The benzylurethane from step 3 (5.54g, 12.76mmol) in 50ml dry THF was cooled to -70^{0}C under nitrogen and 8.80ml of 1.6M nBuLi in hexanes (14.08mmol) added dropwise at the same temperature. After 20 minutes at the same temperature a solution of (R)-glycidyl butyrate (2.00g, 13.88mmol in 5ml THF) was added dropwise and the mixture stirred for 30 minutes at -70^{0}C, and then stirred to ambient temperature overnight. After quenching with 100ml 10% ammonium chloride, the mixture was extracted with EtOAc and usual work-up to give an oily solid, which was purified by flash chromatography (Merck C60 silica, 5% MeOH/dichloromethane eluant) to give a crystalline solid (4.40g, 86%).

MS: ESP+ (M+H) = 401.

^{1}H-NMR (250MHz, DMSO-d6): d = 2.32 (m, 2H), 2.63 (t, 2H), 3.05 (m, 2H), 3.50-3.72 (m,4H), 3.82 (dd,1H), 4.06 (t,1H), 4.73 (m,1H), 5.18 (t,1H), 5.78 (m,1H).

Step 5: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-benzyl-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one

The product of step 4 (2.6g, 6.5mmol), 3-hydroxyisoxazole (0.60g, 7.06mmol), triphenylphosphine (1.96g, 7.48mmol) and diisopropylazodicarboxylate (1.44g, 7.13mmol) in THF (40ml) were reacted using the general method of Example 1. The resultant product was purified by flash chromatograpy (Merck 9385 silica, EtOAc / isohexane (3:2) eluant initially, then repeated using methyl tert-butylether eluant) to give the title product (2.6g, 86%) as a gum. MS: ESP$^+$ $(M+H)^+$= 468.

Step 6 : 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one

The product of step 5 (2.6g, 5.57mmol) in dichloromethane (40ml) was cooled, under an atmosphere of nitrogen, in an ice-water bath then 1-chloroethyl chloroformate (0.80g, 5.59mmol) added dropwise via syringe. The resulting solution was stirred at ice temperature for 1 hour before isolating the intermediate product (carbamate) by flash chromatography (Merck 9385 silica, EtOAc / isohexane (1:1) eluant). The resulting gum was taken up in MeOH (40ml) and refluxed for 1 hour. Evaporation of the solvent after this time gave the title product (1.46g, 64%) as a crystalline solid.

^{1}H-NMR (300MHz, DMSO-d6): δ = 2.54 (m, 2H), 3.27 (m, 2H), 3.72 (m, 2H), 3.92 (dd, 1H), 4.20 (t, 1H), 4.38-4.52 (m, 2H), 5.10 (m, 1H), 5.88 (m, 1H), 6.38 (d, 1H), 7.37 (m, 2H), 8.68 (d, 1H), 9.39 (s(broad), 2H). MS: ESP$^+$ $(M+H)^+$=378.

Step 7: 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(3-t-butoxy-2(S)-hydroxypropanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one

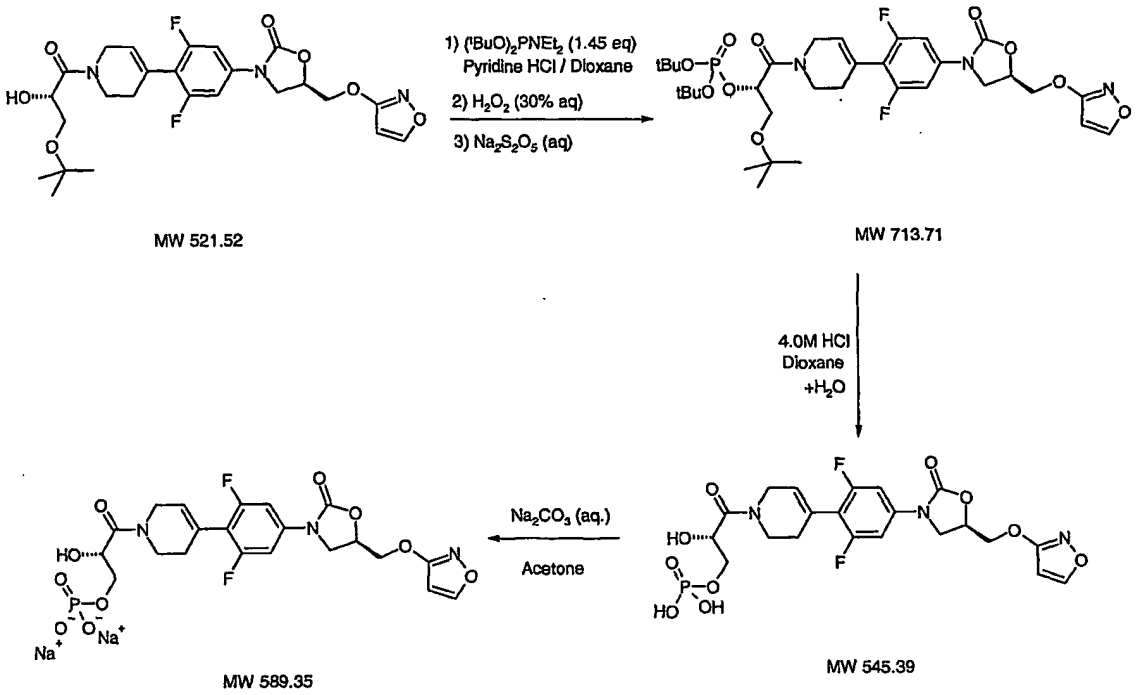
To a stirred solution of the product of step 6 (6.2g, 15mM), N-methyl morpholine (2.27g, 22.5mM), hydroxybenztriazole (2.63g, 19.5mM) and 3-t-butoxy-2(S)-hydroxypropionic acid; (WO Patent 92/00276; 3.16g, 19.5mM) in DMF (60ml) at ambient temperature, was added in portions, dimethylaminopropyl-ethylcarbodiimide (3.73g, 19.5mM). The reaction mixture was stirred for 3hrs.

The solvent was evaporated and the residue was taken into ethyl acetate. It was washed with 2N HCl, water, sat.$NaHCO_3$ and brine, dried over anh.Na_2SO_4 and evaporated to a gum. The title compound was isolated by MPLC (Merck 9385 silica, 60-75% ethyl acetate / isohexane gradient) and crystallised on trituration with ether (6.4g, 82%).

NMR (300Mz, DMSO-d6): δ = 1.11(2s, 9H), 2.34(2s, 2H), 3.43(m, 2H), 3.70(m, 2H), 3.93(d of d, 1H), 4.10(s, 1H), 4.20(t, 1H), 4.28(s, 1H), 4.46(m, 3H), 5.07(m, 2H), 5.88(s, 1H), 6.40(s, 1H), 7.37(d, 2H), 8.70(s, 1H). Mass: ES+ $(M+H)^+$ = 522.

Example

Preparation of Disodium 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2(S)-hydroxy-3-phoshoryl-propanoyl)-1,2,5,6-tetrahydropyridy-4-yl)-3,5-difluorophenyl)oxazolidin--2-one.



The butyl ether obtained as described in preparation 1 (12.5g) was dissolved in 1,4-dioxane (65.2ml) under nitrogen and with stirring. Pyridine (2.63ml) was added with further stirring. The reaction mixture was cooled to 18°C and a solution of HCl in 1,4-dioxane (9.77ml) was added to form a fine suspension of Pyridine.HCl salt in the reaction mixture, whilst keeping the temperature below 25°C.

To this suspension di-t-Butyl N,N-diethylphosphoramidite (9.67ml) was added and the reaction stirred for 1 hour. After cooling again to 18°C, 30% aqueous solution of hydrogen peroxide (4.51ml) was added so as to oxidise the intermediate phosphite to phosphate and the reaction stirred at 25°C for 2 hours. An aqueous solution of sodium metabisulphite (6.29g) was charged to destroy any excess peroxide. The resulting precipitate was filtered, washed with ethyl acetate (50ml) and the filtrates partitioned between ethyl acetate (50ml) and water (12.5ml). The organic layer was brine (37.5ml) washed, the aqueous layer run off. Toluene (25ml) was added to the remaining organic phase which was then distilled under reduced pressure to remove any residual ethyl acetate, and leave the desired phosphate ether as an oil.

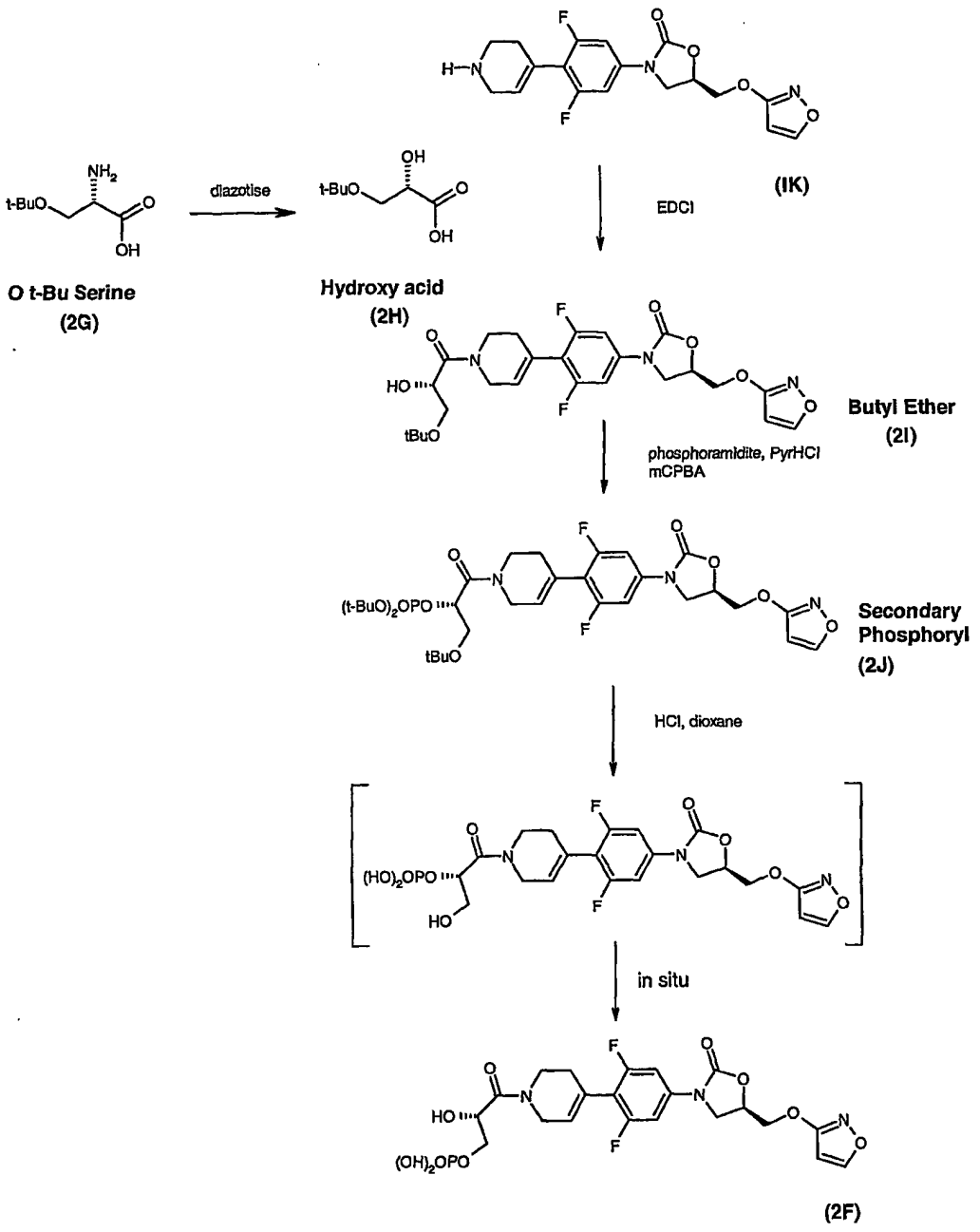
The phosphate ether was charged to a vessel and a small charge of water (4.5ml) added. A solution of HCl in 1,4-dioxane (175ml ~4M) was added and the reaction mixture stirred at 24°C for 25 hours.

HCl and solvent were then removed by distillation under vacuum to afford the desired 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1-(2(S)-hydroxy-3-phoshoryl-propanoyl)-1,2,5,6-tetrahydropyridy-4-yl)-3,5-difluorophenyl)oxazolidin--2-one as an oil.

An aqueous solution of sodium carbonate (4.67g) was added slowly to this oil to generate the di-sodium salt of the phosphate acid. Acetone (187.5ml) was added and a gummy precipitate formed. The resultant suspension was stirred vigorously for at least 1 hour, and then allowed to settle. Solvent was decanted from the vessel, and further acetone (125ml) added and stirred well before decanting again. IMS (Industrial Methylated Spirits 74op) (125ml) was added and the suspension stirred well, the solid filtered off, washed with IMS and dried in the oven to yield the desired product (8.91g, 68%).

Reaction Scheme:

<u>Diol Chemistry : Route to protected diol and rearrangement to primary mono-phosphoryl</u>



Notes :

1. The reaction of (2G) to (2H) is performed under standard conditions, with retention of stereochemistry. The diazotisation reaction may be performed using aqueous

sulfuric acid and aqueous sodium nitrite at ambient temperature. Quenching with sulfamic acid, extraction with TBME and washing with brine gives the (2H) product.

2. The use of the hydroxy acid allows the formation of a protected primary 1,2-diol species. This permits the formation of the secondary phosphoryl compound (2J). Upon treatment with acid (e.g. 4M HCl at ambient temperature) this secondary phosphoryl compound deprotects and then rearranges favourably (possibly via a cyclic intermediate) to the primary phosphoryl compound (2F). The rate of rearrangement is dependant on acid concentration and temperature.

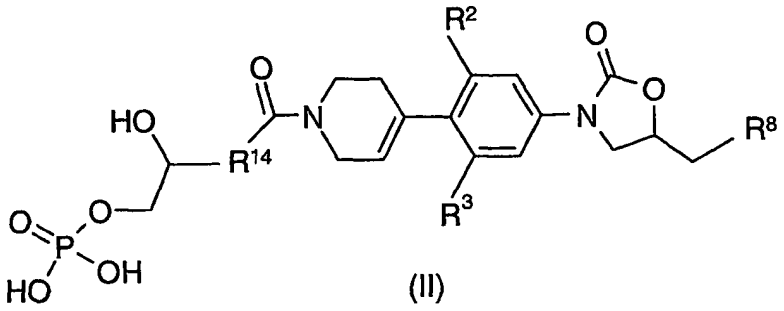
3. Other non-bulky protecting groups in place of t-Bu may be used in (2G) and (2H), for example, any (1-4C)alkyl group; any silyl group (for example trimethylsilyl); or a benzyl group (e.g. using acid catalysed removal, or a reductive removal using e.g. hydrogenation).

4. (2F) may be converted at ambient temperature to, for example, the disodium salt by treatment with 2 mol.eq. or a sodium containing base, in particular sodium carbonate and working-up in acetone and then Industrial Methylated Spirit op74 (IMS).

Claims

1. A method for preparing a compound having a terminal group of formula $(HO)_2OPO$-$CH_2CH(OH)$-CO-, which method comprises treating a species of formula (R^6O-$CH_2CH(OP(O)(OR^7)_2CO$-) (where R^6 is a protecting group, and each group R^7 is hydrogen or a protecting group) with acid in the presence of water to remove any protecting groups R^6 and R^7 and rearrange the secondary phosphoryl group to a primary phosphoryl group.

2. A method according to claim 1 for producing a compound of formula (II)



(II)

or a salt thereof, wherein

R^8 is $-OR^9$, $-SR^9$, $-NHR^{10}$ or $-NR^{11}R^{12}$, where

R^9 is a C-linked 5-membered heteroaryl ring containing 2 to 4 heteroatoms independently selected from N, O and S, which ring is optionally substituted on an available carbon atom by 1 or 2 substituents independently selected from (1-4C)alkyl, amino, (1-4C)alkylamino, (1-4C)alkoxy and halogen, and/or on an available nitrogen atom (provided that the ring is not thereby quaternised) by (1-4C)alkyl; or

R^9 is a C-linked 6-membered heteroaryl ring containing 1 or 2 nitrogen heteroatoms, which ring is optionally substituted on any available C atom (provided that when the N atom is adjacent to the link, there is no substitution on any C atom that is adjacent to this N atom) by 1, 2 or 3 substituents independently selected from (1-4C)alkyl, amino, (1-4C)alkylamino, (1-4C)alkoxy, (1-4C)alkoxycarbonyl and halogen;

R^{10} is is a C-linked 5-membered heteroaryl ring containing 2 to 4 heteroatoms independently selected from N, O and S, which ring is optionally substituted on an available carbon atom by 1 or 2 substituents independently selected from (1-4C)alkyl, amino, (1-4C)alkylamino, (1-4C)alkoxy, (1-4C)alkoxycarbonyl and halogen, and/or on an available nitrogen atom

(provided that the ring is not thereby quaternised) by (1-4C)alkyl;

or

R^{10} is a C-linked 6-membered heteroaryl ring containing 2 or 3 nitrogen heteroatoms, which ring is optionally substituted on any available C atom by 1, 2 or 3 substituents independently selected from (1-4C)alkyl, amino, (1-4C)alkylamino, (1-4C)alkoxy, (1-4C)alkoxycarbonyl and halogen;

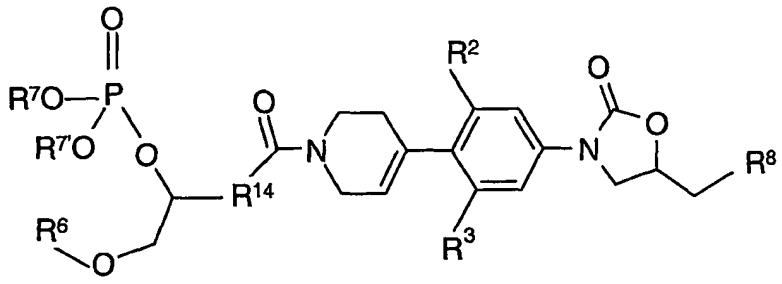
R^{11} and R^{12} together with the nitrogen atom to which they are attached form a 5-membered heteroaryl ring, containing either (i) 1 to 3 further nitrogen heteroatoms or (ii) a further heteroatom selected from O and S together with an optional further nitrogen heteroatom; which ring is optionally substituted on a C atom by an oxo or thioxo group; and/or the ring is optionally substituted on a C atom by 1 or 2 (1-4C)alkyl groups; and/or on an available nitrogen atom (provided that the ring is not thereby quaternised) by (1-4C)alkyl; or

R^{11} and R^{12} together with the nitrogen atom to which they are attached form a 6-membered heteroaryl ring containing up to three nitrogen heteroatoms in total (including the linking heteroatom), which ring is substituted on a suitable C atom by oxo or thioxo and optionally substituted on any available C atom by 1 or 2 (1-4C)alkyl substituents;

R^2 and R^3 are independently hydrogen or fluoro;

R^{14} is a bond or a (1-8C)alkyl group which is optionally substituted by one or more hydroxy groups;

which process comprises reacting a compound of formula (III)



(III)

where R^2, R^3, R^8 and R^{14} are as defined in relation to formula (II), and R^6 is a protecting group and R^7 and $R^{7'}$ are independently selected from hydrogen or a protecting group; with an acid in the presence of water, and thereafter if desired converting the product to a salt.

3. A process according to claim 1 or claim 2 wherein the acid is hydrochloric acid, trifluoroacetic acid or sulphonic acid resins.

4. A process according to any one of the preceding claims which is carried out in an organic solvent which contains from 1 to 10% w/v water.

5. A process according to claim 4 wherein the organic solvent contains from 1-5%w/v water.

6. A process according to claim 5 wherein the organic solvent contains about 3% w/v water.

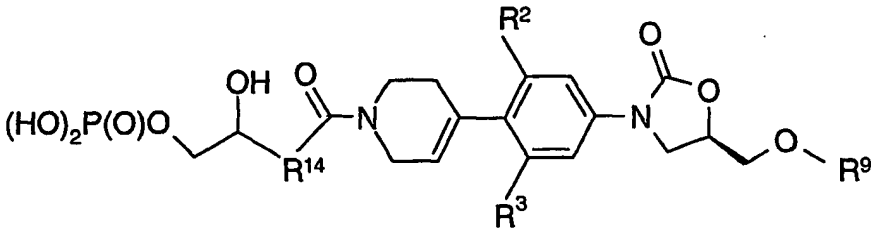
7. A process according to any one of claims 4 to 6 wherein the organic solvent is selected from dioxane or tetrahydrofuran.

8. A process according to claim 7 wherein the organic solvent is dioxane.

9. A process according to any one of claims 2 to 8 wherein in the compound of formula (II), R^8 is a group OR^9.

10. A process according to any one of claims 2 to 9 wherein in the compound of formula (II), where R^8 is a group OR^9 or SR^9 and R^9 is a C-linked 5-membered heteroaryl ring containing 2 to 4 heteroatoms independently selected from N, O and S, which ring is optionally substituted on an available carbon atom by 1 or 2 substituents independently selected from (1-4C)alkyl, amino, (1-4C)alkylamino, (1-4C)alkoxy and halogen, and/or on an available nitrogen atom (provided that the ring is not thereby quaternised) by (1-4C)alkyl.

11. A process according to any one of claims 2 to 10 wherein the compound of formula (II) is a compound of formula (IV)



(IV)

where

R^2, R^3 R^9 and R^{14} are as defined in claim 2.

12. A process according to any one of claims 2 to 11 wherein in the compound of formula (II), R^{14} is a direct bond.

13. A process according to any one of claims 2 to 12 where R^2 and R^3 are fluorine.

14. A process according to any one of claims 2 to 13 wherein R^8 is $-OR^9$, $-SR^9$ or $-NHR^{10}$ and R^9 or R^{10} is isoxazolyl, and particularly isoxazol-3-yl.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 02/02516

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07F9/09 C07F9/6558

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 64417 A (ZENECA LTD.) 16 December 1999 (1999-12-16) cited in the application page 66, line 22 -page 67, line 24	1-14
A	BUCHWALD S L: "Stereochemical evidence for pseudorotation in the reaction of a phosphoric monoester" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US, vol. 106, no. 17, 1984, pages 4916-4922, XP002087111 ISSN: 0002-7863 abstract and scheme 1	1

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
3 September 2002	12/09/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Beslier, L

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 02/02516

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 01 40236 A (ASTRAZENECA AB) 7 June 2001 (2001-06-07) cited in the application the whole document	1-14

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INTERNATIONAL SEARCH REPORT

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